Journal of Cardiology (2009) **53**, 458—462

ELSEVIER

JOURNAL of CARDIOLOGY
Official Journal of the Japanese College of Cardiology
www.elsevier.com/locate/jjcc

CASE REPORT

Vascular Ehlers-Danlos syndrome—All three coronary artery spontaneous dissections

Michinari Nakamura (MD)[a,*], Junji Yajima (MD)[a], Yuji Oikawa (MD)[a], Ken Ogasawara (MD)[a], Tokuhisa Uejima (MD)[a], Keiko Abe (MD)[b], Tadanori Aizawa (MD, FJCC)[a]

[a] *Department of Cardiology, The Cardiovascular Institute, 7-3-10 Roppongi, Minato-ku, Tokyo 106-0032, Japan*
[b] *Department of Pathology, Tohoku University Graduate School of Medicine, 2-1 Seiryo-machi, Aoba-ku, Sendai-shi 980-8575, Japan*

Received 10 August 2008; accepted 11 September 2008
Available online 8 November 2008

KEYWORDS
Vascular Ehlers-Danlos syndrome;
Connective-tissue disorder;
Acute coronary syndrome;
Spontaneous coronary artery dissection

Summary Vascular Ehlers-Danlos syndrome is an inherited connective-tissue disorder causing arterial and gastrointestinal fragility and spontaneous rupture of the large arteries, uterus, or bowel. Among arterial dissections and ruptures, spontaneous coronary artery dissection is extremely rare in this disorder. The specific therapeutic strategy for this disorder and its complications has not yet been established. In this report, we describe a 33-year-old woman with all three coronary artery spontaneous dissections, resulting in cardiogenic shock and therapy-resistant ventricular fibrillation. We could successfully complete revascularization of all three coronary arteries and terminate the life-threatening arrhythmia. Biochemical findings finally revealed a point mutation in the *COL3A1* gene, consistent with a diagnosis of vascular Ehlers-Danlos syndrome. To the best of our knowledge, this is the first case of vascular Ehlers-Danlos syndrome causing all three coronary artery spontaneous dissections. Our case also suggests that, from vascular fragility even if it is spontaneous coronary dissection, physicians always consider connective-tissue disorders as a differential diagnosis at an early stage even though that would be a first complication, and percutaneous coronary intervention with stenting using intravascular ultrasound could be a strategic option for even repeated and fatal spontaneous coronary artery dissections in vascular Ehlers-Danlos syndrome.

Introduction

Spontaneous coronary artery dissection is uncommon, but has been increasingly recognized as

* Corresponding author. Tel.: +81 3 3408 2151; fax: +81 3 3401 0469.
E-mail address: nmichi-kyu@umin.ac.jp (M. Nakamura).

0914-5087/$ — see front matter © 2008 Japanese College of Cardiology. Published by Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.jjcc.2008.09.007

an important cause of acute coronary syndrome or sudden death. Though spontaneous coronary dissection typically affects young women during the peripartum period without cardiovascular risk factors, the pathophysiology remains unclear. Meanwhile, connective-tissue disorders underlie spontaneous coronary dissection in some cases. Pregnancy-related deaths in patients with vascular Ehlers-Danlos syndrome (Ehlers-Danlos syndrome type IV) reach 14.8% [1]. Most patients with vascular Ehlers-Danlos syndrome survive the first and second major complications; however, after repeated cardiovascular events, the clinical outcome of vascular surgery remains unsatisfactory. Spontaneous coronary artery dissection in patients with vascular Ehlers-Danlos syndrome is very rare, and also treatment for this disorder and the therapeutic strategy for its complications have not yet been established. We herein report a patient with vascular Ehlers-Danlos syndrome, undergoing the fifth systemic manifestation including spontaneous dissections of all three coronary arteries.

Case report

A 33-year-old woman, who was born to a Japanese mother and an American father, without traditional coronary risk factors presented with bilateral lower jaw pain 4 months after cesarean section at her first pregnancy due to the rupture of a splenic artery aneurysm. A similar symptom had been experienced 4 years ago. She was referred to our hospital for more investigations 2 weeks after the onset of the symptom.

There was no history of ischemic heart disease or sudden death in her family. Her physical examination results were within normal limits, including clinically significant craniofacial findings. T wave was inverted in leads II, III, aV_F, and $V_{5\text{-}6}$ in the electrocardiogram. Troponin I (0.2 ng/mL) remained slightly elevated. Delayed enhanced magnetic resonance imaging (MRI) revealed two separate regional enhancements in the anterior and inferolateral walls, indicating two previous myocardial infarctions. Coronary angiography revealed the dissection of the posterolateral branch of the left circumflex coronary artery (LCx); therefore, intervention was not performed. She was treated with medications including aspirin, nicorandil, and an angiotensin II-receptor blocker.

Two weeks later, however, she suffered sudden precordial chest pain, when the electrocardiogram showed ST segment elevation in leads $V_{1\text{-}5}$. Urgent coronary angiography revealed both dissection and total occlusion of the left anterior descending artery (LAD) and dissection of the right coronary artery (RCA) (Fig. 1). Intravascular ultrasound (IVUS), which had been previously reported to be helpful in diagnosing spontaneous coronary artery dissection [2], revealed a prominent dissection flap with a false lumen (Fig. 2). Because of preserved blood flow in the RCA, coronary angioplasty with stenting of only the LAD was performed, which required intra-aortic balloon pumping (IABP) and percutaneous cardiopulmonary support (PCPS). Even after successful angioplasty, therapy-resistant ventricular fibrillation repeatedly occurred. Therefore, a second coronary angiography was performed after 6 h, which revealed the dissection of the LCx. Spontaneous dissections at the RCA and the LCx were successfully treated with stenting using IVUS, and the termination of the life-threatening arrhythmia after complete revascularization in all three coronary arteries made her vital signs remain stable.

Several hours later, however, bleeding in both the retroperitoneal and abdominal cavities suddenly occurred. Computed tomography showed rupture of the right common iliac artery, but no surgical intervention for this rupture could have been a strategic option in this case because of systemic and severe fragile vessels. Disseminated intravascular coagulation promoted massive hemorrhage, resulting in multiple organ failure, and unfortunately the patient died during hospitalization.

Autopsy revealed severe thinning and fragility of the aortic wall. Pathological findings disclosed medial degeneration in the systemic arteries, suggesting the cause of dissection may have been connective-tissue disorders (Fig. 3). The diagnosis of vascular Ehlers-Danlos syndrome, was confirmed by the identification of a point mutation (c.1988G > A), in one allele of the *COL3A1* gene. A single nucleotide change resulted in the substitution of aspartic acid for glycine (G496D) within the triple helical region of the type III collagen molecule.

Discussion

Vascular Ehlers-Danlos syndrome is an autosomal dominant connective-tissue disorder, resulting from mutations affecting the *COL3A1* gene encoding for type III procollagen synthesis. The estimated prevalence of the Ehlers-Danlos syndromes varies between 1/10,000 and 1/25,000 with no ethnic predisposition, and among all Ehlers-Danlos syndromes, vascular Ehlers-Danlos syndrome accounts for approximately 5—10% of cases. The clinical diagnosis of vascular Ehlers-Danlos syndrome is made

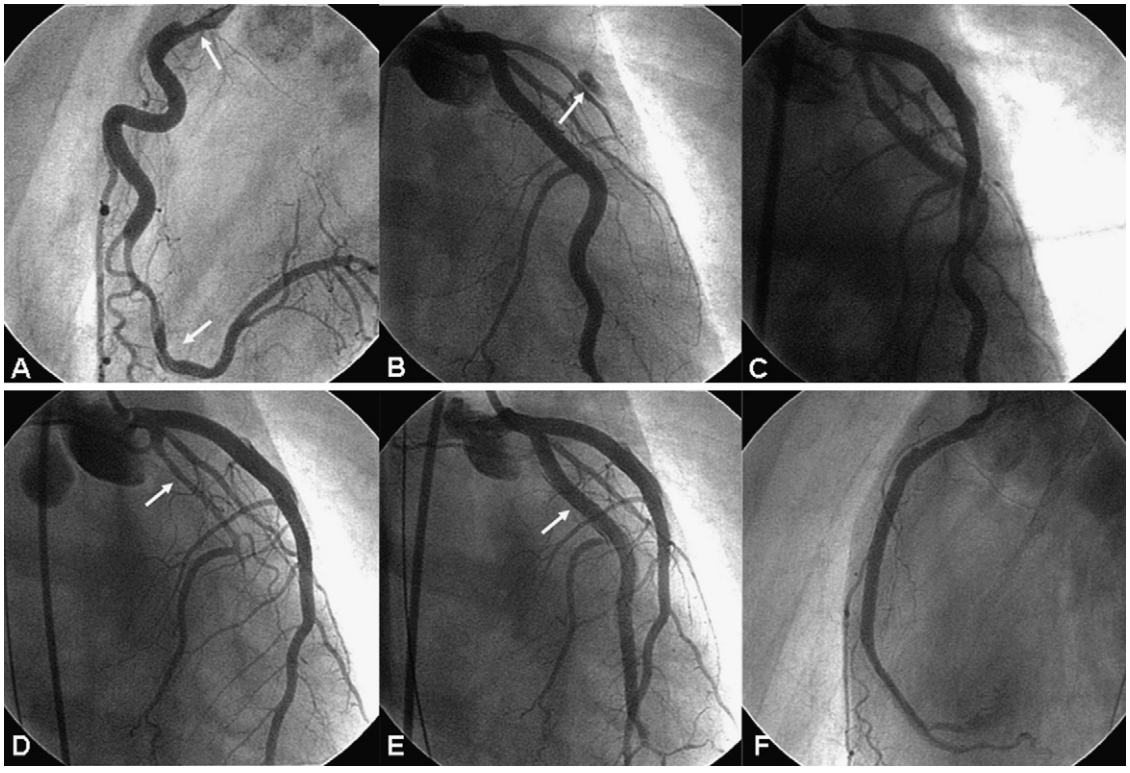

Figure 1 Coronary angiography showing (A) the dissecting right coronary artery (RCA), (B) the left coronary artery and dissection starting from the proximal site of the left anterior descending coronary artery (LAD) associated with contrast agent pooling and the distal total occlusion, (C) the LAD after stenting, (D) the dissecting left circumflex coronary artery (LCx), (E) the left coronary artery after stenting, and (F) the RCA after stenting.

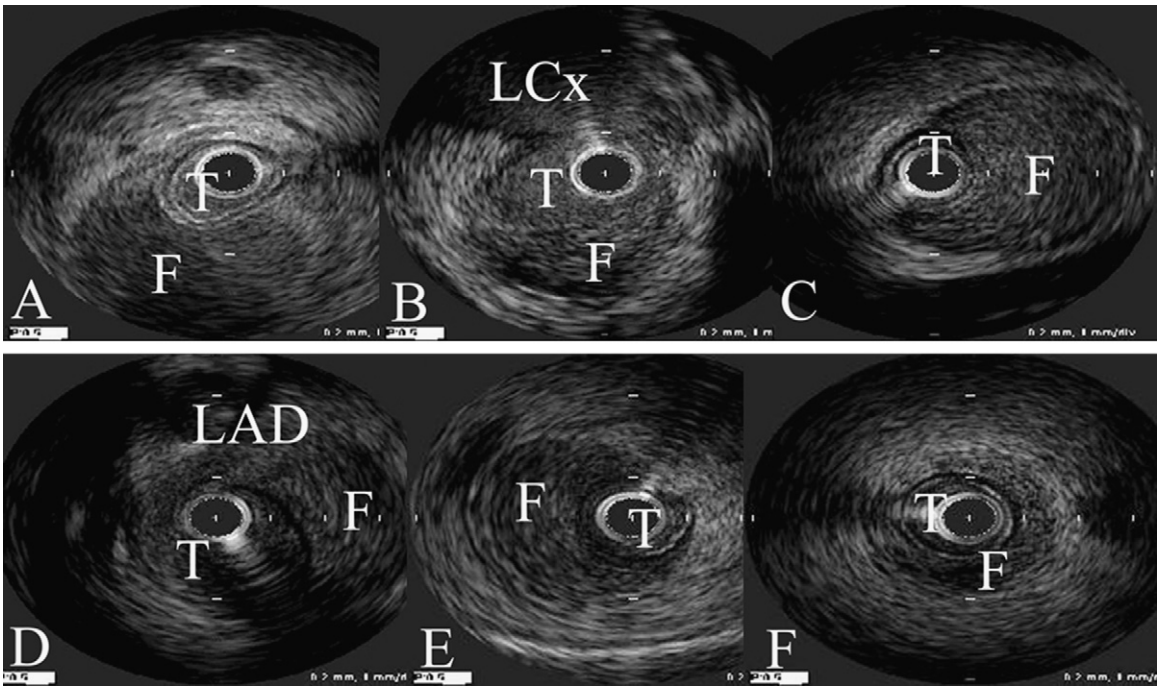

Figure 2 Intravascular ultrasound showing a dissecting intramural hematoma in a false lumen [F] and collapse of the true lumen [T]. (A) The distal LAD, (B) the proximal LAD, (C) the distal LCx, (D) the proximal LCx, (E) the distal RCA, and (F) the proximal RCA.

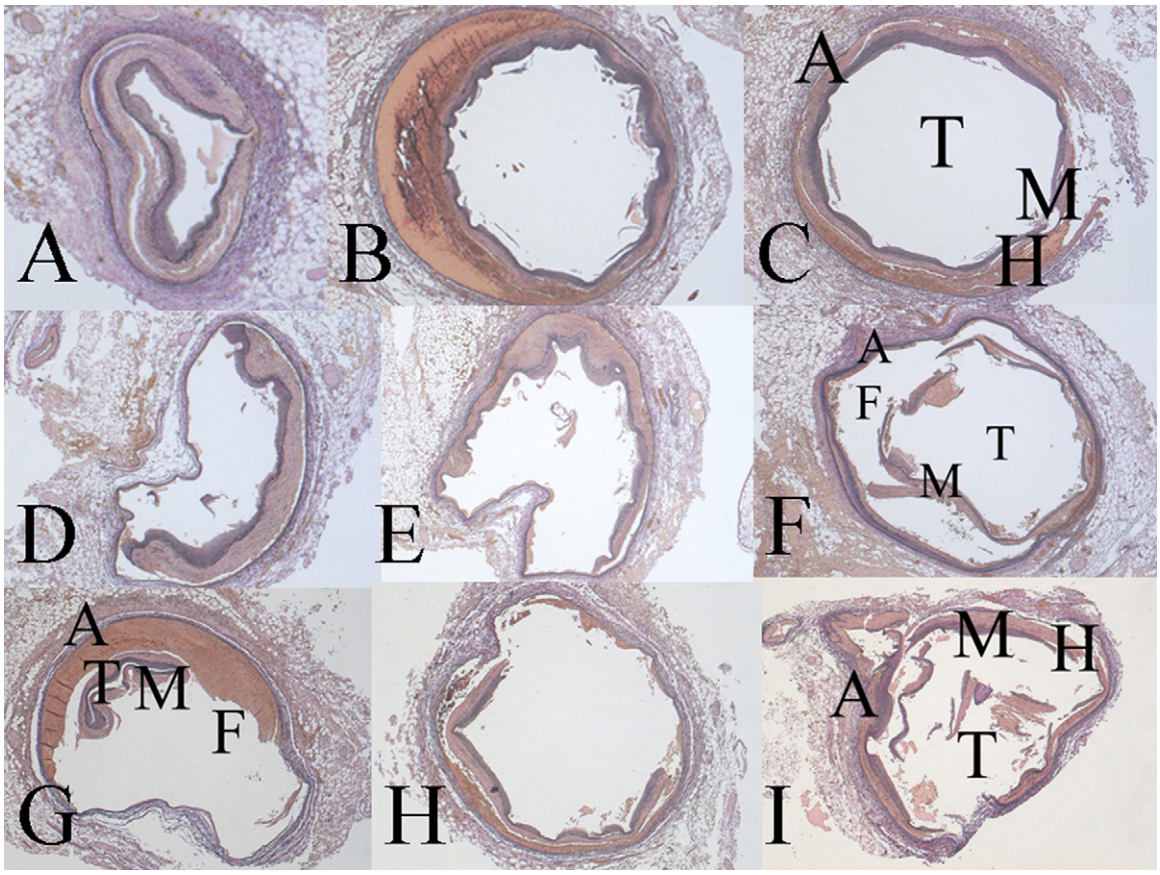

Figure 3 Sections from the coronary arteries showing a dissecting intramural hematoma [H] in false lumen [F] between adventitia [A] and media [M], collapse of the true lumen [T], and medial degeneration with marked elastin fragmentation, stained with EVG stain (x12.5). (A) The distal LAD, (B) the mid LAD, (C) the proximal LAD, (D) the distal LCx, (E) the mid LCx, (F) the proximal LCx, (G) the distal RCA, (H) the mid RCA, and (I) the proximal RCA.

based on the finding of at least two of four clinical criteria: easy bruising, thin skin with visible veins, characteristic facial features, and rupture of arteries, uterus, or intestines, but molecular studies are required for confirmation [3]. According to the previously published articles including case reports, surgical interventions such as coronary artery bypass grafting and heart transplantation, percutaneous coronary intervention with stenting, and only observation without invasive intervention could be strategic options for spontaneous coronary artery dissection; however, until now, management and treatment for the disorder and therapeutic strategy for its complications have not yet been established, especially in repeated and fatal dissections [3,4].

Spontaneous coronary artery dissection was first described in a 42-year-old woman at autopsy in 1931 [5]. No single etiology completely explains the pathogenesis. There are a number of associated conditions such as pregnancy, abnormal transforming growth factor-beta signaling (e.g., Marfan syndrome, vascular Ehlers-Danlos syndrome, and Loeys-Dietz syndrome [6]), oral contraceptive use, sexual intercourse, cocaine abuse, vasculitis (e.g., Churg-Strauss syndrome), and intense physical exercise. The pathology is also not specific, but eosinophilic periadventitial inflammation was observed in some cases, and cystic medial necrosis or medial degeneration was observed in others.

Our patient had no craniofacial features of vascular Ehlers-Danlos syndrome, which are not indispensable for diagnosis of the disease, but help diagnosis at an early age. The first manifestation might be an anterior myocardial infarction due to spontaneous dissection of the LAD, which was thought to be completely healed, at the age of 29, presumed by echocardiography and delayed enhanced MRI. The age was similar to the average age of the first manifestation reported previously (23.5 years) [1]. The second was a splenic aneurysm rupture at the age of 33 years in the last trimester of pregnancy, then 4 months later, an inferolateral myocardial infarction, all three coronary artery dis-

sections, and the rupture of the right common iliac artery. The age at death (33 years) was younger than the median survival of vascular Ehlers-Danlos syndrome (48 years) [1] mostly because the survival depends on the dissection site and severity of ischemia, and in this case, her complications occurred in coronary arteries. However, the dissection or rupture site cannot be predicted and there seems to be no relation between location of the mutation in the *COL3A1* gene and the type of manifestations [1].

The first angiographic finding of the distal LCx dissection made us decide on medical therapy because spontaneous dissection had been previously reported to be completely healed with medical therapy, or observation in some cases [7,8], but after multiple coronary artery dissections, we had to choose invasive intervention with support of IABP and PCPS due to ongoing ischemia and therapy-resistant ventricular fibrillation. Although among arterial dissections in vascular Ehlers-Danlos syndrome coronary artery dissection is extremely rare because vascular complication has a tendency toward arteries of large and medium diameter [1,9], three of the patient's vascular complications were spontaneous coronary dissections.

Autopsy revealed that the site of rupture in the right common iliac artery was separated from the puncture site, but it is unclear whether invasive intervention including IABP and PCPS somewhat influenced the dissection; therefore, for fragile vessels, simpler and more careful procedures should be demanded.

Vascular Ehlers-Danlos syndrome is unfamiliar, but once started, cardiovascular manifestations are catastrophic. Angiotensin II-receptor blockers, beta-blockers, exercise restrictions, frequent cardiovascular imaging, or vascular surgery is insufficient for 'dissection storm', that is, repeated dissections in rapid succession. The trigger of dissection and/or rupture in rapid succession is unknown, but pregnancy and some hormonal unbalance are thought to be the causes. Although spontaneous coronary artery dissection is a rare event in vascular Ehlers-Danlos syndrome, if the first complication is coronary artery dissection, cardiologists and emergency care physicians should pay attention to tissue or vascular fragility and suspect connective-tissue disorders. A skin biopsy and molecular testing should be performed as soon as possible because a vascular manifestation is always life-threatening.

In conclusion, we reported the first case of vascular Ehlers-Danlos syndrome undergoing spontaneous all three coronary artery dissections that was resolved by full-coverage bare-metal stenting of the dissection sites using IVUS. Our case indicates that even in vascular Ehlers-Danlos syndrome, percutaneous coronary intervention can be therapeutic strategy for repeated and severe coronary artery dissections with ongoing fatal ischemia.

Acknowledgment

We would like to thank Dr Peter Byers of the University of Washington for the molecular testing.

References

[1] Pepin M, Schwarze U, Superti-Furga A, Byers PH. Clinical and genetic features of Ehlers-Danlos syndrome type IV, the vascular type. N Engl J Med 2000;342:673—80.
[2] Maehara A, Mintz GS, Castagna MT, Pichard AD, Satler LF, Waksman R, et al. Intravascular ultrasound assessment of spontaneous coronary artery dissections. Am J Cardiol 2002;89:466—8.
[3] Beighton P, De Paepe A, Steinmann B, Tsipouras P, Wenstrup RJ. Ehlers-Danlos syndromes: revised nosology, Villefranche, 1997. Ehlers-Danlos National Foundation (USA) and Ehlers-Danlos Support Group (UK). Am J Med Genet 1998;77:31—7.
[4] Germain DP. Ehlers-Danlos syndrome type IV. Orphanet J Rare Dis 2007;2:32.
[5] Pretty HC. Dissecting aneurysm of a coronary artery in a woman aged 42. BMJ 1931, i:667.
[6] Loeys BL, Schwarze U, Holm T, Callewaert BL, Thomas GH, Pannu H, et al. Aneurysm syndromes caused by mutations in the TGF-beta receptor. N Engl J Med 2006;355:788—98.
[7] Trabattoni D, Calligaris A, Bartorelli AL. Fast and complete healing of 2 coronary artery spontaneous dissections. Circulation 2005;111:e282.
[8] Milhous JG, van der Heyden J, ten Berg JM. Images in cardiology. Spontaneous healing of a severe coronary artery dissection. Heart 2006;92:692.
[9] Oderich GS, Panneton JM, Bower TC, Lindor NM, Cherry KJ, Noel AA, et al. The spectrum, management and clinical outcome of Ehlers-Danlos syndrome type IV: a 30-year experience. J Vasc Surg 2005;42:98—106.